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Editing EU legislation to fit plant genome editing

The use of genome editing technologies in plant breeding requires a novel regulatory approach for new plant varieties that involves farmers

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In light of the ongoing discussion in the EU whether new plant varieties generated by genome editing are genetically modified organisms (GMOs) or not, we propose a novel approach for regulating plant breeding in general. Our proposal involves a flexible and scalable system that is capable of adapting to the rapid evolution of new technologies such as genome editing. It proposes an operational method that accounts for traditional and novel technologies, and a dynamically scalable risk assessment, which focuses on the phenotype of a novel breed instead of the method used to generate it. This approach would also resolve various dichotomies in the current debate, namely declaring new genome editing methods as highly efficient, while ignoring the impact of yet unknown risks, and proposing exemptions from regulation on the basis of the type of DNA created, whereas an older technology with fully characterized risks would still carry a heavy regulatory burden. Our proposal also takes into account that any new risk paradigm must be understood and accepted by the public, suggesting a greater role for farmers in ensuring the safe use of new breeding technologies.

Definitions

There are various guidelines and regulations worldwide used to assess the risks of genetically modified crops (see Further Reading Box 1 for USA and Canada), but the EU's regulatory framework arguably has the biggest impact given the size of the market and given its influence on other jurisdictions around the world. In 1990, the EU adopted its first regulatory framework, replaced in 2001 by Directive 2001/18/EC "on the deliberate release into the environment of genetically modified organisms" (GMO). According to Article 2, a GMO "means an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination". However, "the techniques listed in Annex I A, part 2, are not considered to result in genetic modification" (namely, *in vitro* fertilization, and "natural" processes such as conjugation, transduction, transformation, and polyploidy induction). Article 3 lists further exceptions for which the Directive shall not apply, namely mutagenesis, and "cell fusion of plant cells of organisms which can exchange genetic material through traditional breeding methods".

> *"... EU regulation is based on the process of generating plant varieties rather than the phenotype, and it further distinguishes based on the DNA structure ..."*

In summary, EU regulation is based on the process of generating plant varieties rather than the phenotype, and it further distinguishes based on the DNA structure, which should not occur "naturally". It includes vaguely formulated familiarity-based exemptions ("genetic modification, which have conventionally been used in a number of applications and have a long safety record"), but no enabling mechanism for future exemptions. This regulation was explicitly adopted to allow the use of biotechnology when proven safe, but it has worked against innovation and facilitated massive disinformation, primarily because public debates are centered on the legal concept of "GMOs", without case-by-case discrimination.

The problems with the EU regulation

The discovery of natural horizontal gene transfer in plants (www.biofortified.org/tag/natural-gmos/page/2/) and the case of naturally transgenic sweet potato [1] have raised questions about the relevance of the EU regulation and its concept of "natural". In sweet potato, *Agrobacterium*-derived genes became stably incorporated and inherited across generations. These discoveries also challenge the concept of "plant breeders' gene pool" used by EFSA to distinguish between conventional breeding and cisgenesis from transgenesis according to the "sources of genes" (www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/2561.pdf)

This dubious concept of "natural" has also spread beyond Europe and was recently adopted in the GMO labeling bill by the US Senate and House of Representatives: "The

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Box 1: Further reading

The plant biotechnology regulatory framework in Canada and the USA

The Canadian Food Inspection Agency developed the concept of "plant with 'novel' trait" ("*Not only does this definition capture GMOs, it also includes induced mutations, natural mutations and exotic germplasm that have not previously been grown in Canada*").

Sprink T, Eriksson D, Schiemann J, Hartung F (2016) Regulatory hurdles for genome editing: process- vs. product-based approaches in different regulatory contexts. *Plant Cell Rep* **35**: 1493–1450

A genome-edited (oligonucleotide-directed mutagenesis) herbicide-tolerant canola is already authorized since 2013 by the Canadian Food Inspection Agency (http://www.inspection.gc.ca/plants/plants-with-novel-traits/approved-under-review/decision-documents/dd-2013-100/eng/1427383332253/1427383674669) and in the USA.

Fladung M (2016) Cibus' herbicide-resistant canola in European limbo. *Nat Biotechnol* **34**: 473–474

In the USA, the regulatory trigger is process based, but the performed risk assessment is product based (depending on the trait and the host organism, one, two, or three federal agencies, FDA, EPA, and APHIS, examine whether these products present risk to humans, animals, or the environment). The USA used existing regulation for assessing the risks of biotechnology.

Conko G, Kershen DL, Miller H, Parrott WA (2016) A risk-based approach to the regulation of genetically engineered organisms. *Nat Biotechnol* **34**: 493–503

term 'bio-engineering'[...] refers to [...] genetic material that has been modified through *in vitro* recombinant deoxyribonucleic acid (DNA) techniques; and for which the modification could not otherwise be obtained through conventional breeding or found in nature" (www.agriculture.senate.gov/imo/media/doc/Ag%20biotech%20compromise%20proposal.pdf).

Another inconsistency of the EU's regulation is the fact that similar traits, such as herbicide tolerance, are defined as GM when obtained by transgenesis, but not when obtained by mutagenesis. When mutagenesis is performed *in vitro* and the gene is re-introduced by transgenesis, the host becomes a GMO, but not when the mutation occurs "naturally". This is the case for the weed *Eleusine indica*, which became resistant to glyphosate via two point mutations [2], whereas the same targeted mutations, which were transferred by transgenesis, make herbicide-tolerant maize a GMO.

A meaningless definition of a GMO

As there is mounting criticism of this "nonsensical" definition of what is and is not a GMO, the definition itself, namely the above-mentioned passages of the EU Directive, was subjected to semantic analyses to determine when new breeding technologies (NBT) should be considered as GMOs (see Further Reading Box 2). A first opinion proposes to distinguish between newly generated DNA sequences, depending on whether or not they could occur "naturally". This is in line with the EU Directive that excludes mutation-based breeding from regulation. However, it disregards the fact that the occurrence of mutations is simply a matter of probability. Gene editing to generate longer DNA constructs—the length of which are being arbitrarily determined—or introducing "foreign" DNA would still be considered GM, disregarding the fact that, as the sweet potato case has shown, such a definition can be shaky. This first option will continue to be controversial since mutational edits of a native gene, to create herbicide tolerance, for example, would be exempted from regulation, whereas transferring the same gene into a closely related species by transgenesis would not. In our opinion, the hope of some laboratories to avoid controversy by avoiding a GMO status for certain products is an illusion. A second opinion proposes that we adopt a strict process based, precautionary approach to regulate all NBTs as GMOs. This would have disastrous effects on the usage of these technologies in the future.

Both options would have detrimental consequences for research and for the development of new plant varieties. This has likely contributed to the EU's foot-dragging in deciding whether a gene-edited product is a GMO or not, including making a decision on the simple case of herbicide-resistant canola developed by Cibus (see Further Reading Box 1). The above-mentioned sweet potato also illustrates how disconnected from reality both proposals are. This species is not considered a GMO, but if somebody removed its natural transgenes by gene editing, it would become a GMO following option 2. It would also become a GMO following option 1 too if one considers these deletions would have been unlikely to occur by "natural recombination".

A third regulatory option, and in our opinion the most reasonable one, would abandon the whole GMO concept in favor of a product-based legislation. Admittedly, this would take years, but it has already taken years for the EU to decide whether the Cibus canola is GM or not.

Different risks

The main difference between gene editing techniques and transgenesis is that the first method targets a predefined region of the genome, which has created new options for precision breeding and crop improvement. However, there is still a possibility for off-target mutations, even if these occur less frequently than with most other techniques. The example of naturally occurring herbicide tolerance also shows that gene editing has the same implications for environmental risk assessment as other techniques, whether mutagenesis, cisgenesis, or transgenesis.

Considering that NBT can either induce a point mutation as mutagenesis does, silence a gene, or even transfer gene(s) between species, a sound safety assessment should not be based on the process which option 2 would entail. Considering the extent of DNA modification needed to create a binary classification of GMO vs. non-GMO as in option 1, it would also not be in line with the actual risks. Of course, a novel breeding method that creates precise micro-mutations would require a lower level of risk assessment and could be cleared after a short evaluation period, but this depends on the trait and its associated risks.

Product-based regulation

Many scientific organizations in Europe (see Further Reading Box 3) therefore recommend that the EU should regulate plant varieties based on their specific agricultural traits and/or product, and not on the technical process. However, there are different definitions for "product", because some articles (see Further Reading Box 3) consider the DNA construct to be a "product". This led some authors to conclude that the EU regulation is both process based and product based because it includes a mention of "the genetic material" generated by using a genetic modification

Box 2: Further reading

Legal analysis of the same Directive lead to divergent views whether NBTs produces "GMOs"

The Swedish Board of Agriculture (http://www.teknat.umu.se/english/news//.cid259265) and the German Federal Office of Consumer Protection and Food Safety (http://www.bvl.bund.de/SharedDocs/Downloads/06_Gentechnik/Opinion_on_the_legal_classification_of_New_Plant_Breeding_Techniques.pdf), for example, and some lawyers proposed to distinguish between DNA sequences produced by gene editing, depending on whether they could occur "naturally" (by mutagenesis) or not.

In contrast, the opinion commissioned by the German Federal Agency for Nature Conservation (http://bfn.de/fileadmin/BfN/agrogentechnik/Dokumente/Legal_analysis_of_genome_editing_technologies.pdf), and other lawyers proposed to regulate all NBTs as GMOs.

Criticisms of the "nonsensical" definition of GMOs

Tagliabue G (2015) The nonsensical GMO pseudo-category and a precautionary rabbit hole. *Nat Biotechnol* **33**: 907–908

Tagliabue G (2016) The meaningless pseudo-category of "GMOs", *EMBO Rep* **17**: 10–13

Johnson N (2015) http://grist.org/food/mind-bomb-its-practically-impossible-to-define-gmos/

Miller HI (2016) What's in a name? Plenty, if it's a 'GMO.' http://www.nationalreview.com/article/438082/gmo-labeling-unnecessary-meaningless-and-misleading

process, which "does not occur naturally". The process versus product debate is semantically confusing.

This would not be the case if product was defined as "final product" or "phenotype". For example, an herbicide tolerance phenotype should be assessed based on the product, and the possibility of gene flow within the plant species. Numerous protocols, for instance OECD and EFSA guidelines, are available for conducting safety assessments. These can be chosen on a phenotype-by-phenotype basis and can be adapted to the evolution of NBTs. Alternative approaches such as *in vitro* omics techniques could also be used on a case-by-case basis, although they cannot yet replace existing risk assessment methods. What should be avoided is insisting on risk assessment techniques that are neither necessary nor adequate for the phenotype.

In 1997, Barton *et al* [3] presented a "Stanford model" for a risk-based system to regulate field trials, which could be used as inspiration for the EU. This model offers guidelines for the classification of products into risk categories taking potential harm and the likelihood of harm into account [4]. Unfortunately, Europe is politically locked in its misinterpreted Precautionary Principle and is unable to address the issue of NBT and genetic engineering in general.

A new paradigm for regulation

First, regulation should be based on the final trait, that is, the phenotype of the plant, rather than on the technique or the "naturalness" of the DNA insertion. All modern plant breeding techniques, including marker-assisted selection, should enter the risk assessment from the same starting line. This should not become a marathon, as is currently the case in the EU: In most instances, the "race" to approval would be short if it were based on real risk.

Second, the current risk paradigm needs to change. The debate should shift away from demonstrating that "GM technology is safe" [5,6], since no human activity is intrinsically safe. Modern plant breeding does not bear specific risks. However, biosafety protocols are required, especially for novel technologies. But the protocols should be adapted to each trait, be flexible (dynamically scalable), and revisable [4,7], which is incompatible with the current fixed rule. A thorough and repetitive risk assessment for each event and each individual genetic modification would be no longer necessary if products of the same class and species had already been assessed [4,8]. Furthermore, *ex ante* risk assessment should, whenever possible, be gradually replaced by the adoption and monitoring of good agricultural practices, as well as implementing precision agriculture. Finally, one should also take into account that not implementing a technology could also bear risks.

Third, rather than blocking a technology until proven as risk-free—an impossible task—its potential benefits should be prioritized if risks are reasonably low. However, political authorities or policymakers should not attempt to predict all benefits; for instance, the reduced mycotoxin contamination of *Bt*-maize was not foreseeable. Instead, policymakers should define a general agricultural policy, and agricultural biotechnology should contribute to this policy. A given technology should only be banned if it proves to contradict policy goals. Last but not least, policymakers should abandon the idea of deciding what a "genetic modification" is by law, since the concept is constantly evolving with new scientific discoveries.

A scalable framework for risk assessment

Any new plant events would have to be authorized for use and marketing in the EU. Anyone seeking authorization—biotech companies, breeders, academic institutions, or even farmers—proposes a risk classification based on the species and on the phenotype: herbicide-tolerant, pest-resistant, drought-resistant, nutritional fortification, and so on. If the classification is accepted, the new trait will be subjected to the appropriate risk assessment, which will examine the consequences of using it, and determine the potential threats and known vulnerabilities in terms of human and animal health, and environmental impact.

The scale of the risk assessment should be determined rationally with clear goals and objectives that are both understood and accepted by the public. These goals and objectives will of course generate much discussion, and even resistance, depending on the lack of trust in political authorities, and by activists set to prevent the authorization of any GMOs. Therefore, innovative new tools are needed to generate broad public consensus regarding the use of NBTs in agriculture.

It might, for example, include a tool to assess the credibility of risk assessment procedures that evaluate the ability of risk assessment frameworks to deal with a wide variety of possible scenarios: What assets should be protected? What are the threats? What are the consequences? Which emergency measures can be taken if something goes wrong? Importantly, these are questions that the public can easily understand. To further rationalize this credibility tool, it should use past information about the use of plant varieties to strengthen or reduce the burden of risk assessment on the basis of experience. For example, such a database could facilitate the understanding that animal feeding studies are no longer necessary for

Box 3: Further reading

The semantically confusing process vs. product debate

Huang S, Weigel D, Beachy RN, Li J (2016) A proposed regulatory framework for genome-edited crops. *Nat Genet* **48**: 109–111

Araki M, Ishii T (2015) Towards social acceptance of plant breeding by genome editing. *Trends Plant Sci* **20**: 145–149

Sprink T, Eriksson D, Schiemann J, Hartung F (2016) Regulatory hurdles for genome editing: process- vs. product-based approaches in different regulatory contexts. *Plant Cell Rep* **35**: 1493–1450

Scientific authorities recommending the EU to regulate the "product" (understood as specific agricultural trait or phenotype), not the technical process

UK Advisory Committee on Releases to the Environment (ACRE), Report 1 (2013) https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/239839/an-evidence-based-regulatory-system-for-gmos.pdf

UK House of Commons Science and Technology Committee (2015) http://www.publications.parliament.uk/pa/cm201415/cmselect/cmsctech/328/328.pdf

Germany's National Academy of Sciences (Nationale Akademie der Wissenschaften Leopoldina, 2015) http://www.leopoldina.org/uploads/tx_leopublication/2015_3Akad_Stellungnahme_Genome_Editing_01.pdf

European Academies' Science Advisory Council (EASAC, 2012, 2015) http://www.epsoweb.org/file/2105

European Plant Science Organisation (EPSO, 2015), representing more than 220 research institutes and universities from 28 European countries http://www.epsoweb.org/file/2147

This reasoning is not limited to plants: Carroll *et al* recently presented arguments for a regulation based on products not process in the case of hornless cattle.

Carroll D, Van Eenennaam AL, Taylor JF, Seger J, Voytas DF (2016) Regulate genome-edited products, not genome editing itself. *Nat Biotechnol* **34**: 477–479

"classic" transgenic plants [9] and that no allergenic reaction has been shown for any marketed transgenic products, but that scrutiny is still necessary, because allergenicity has been observed in experimental plants. A comprehensive risk metrics would allow citizens to understand the *actual* risks and the risk assessment procedures. However, this cannot be achieved without a change in political thinking.

The whole edifice of EU regulation is based on two misguided assumptions. First, that experts and technocrats know better and should therefore draft and develop regulations and directives. This assumption has obviously inspired the current regulation of GMOs. Second, that this technocratic power—which is often criticized for being "non-democratic"—should be validated by a democratic process, which in reality is often influenced by various "stakeholders" in a "misplaced" democracy. Lobby groups, including political groups inspired by "green" ideology, became very influential in this postmodern travesty of democracy that led us to the current situation [10]. This top-down approach, influenced by intense lobbying by interested parties, has obviously failed to achieve its original goal, namely implementing agricultural biotech in a free market when recognized as safe. It has created a costly, inefficient, burdensome, and illogical regulatory system, and it has propagated unfounded fears about GM technology.

Under public pressure, politicians have continued to increase the regulatory burden to assess perceived risks, and have even directly interfered with scientific risk assessment. Instead, political authorities should use a democratic procedure to establish the level of risk that is tolerable by society at-large. They should not focus on pseudocategories like "GMO" or deceptive concepts like "natural", but on objective goals: production, sustainability, environmental impact, biodiversity, and so on.

A greater role for farmers

Costly and burdensome risk assessments of new NBTs have been preventing small- to medium-sized companies, and academic laboratories to bring new products to the market. We therefore propose to reduce the pre-marketing assessment of hypothetical environmental risks, and instead enable farmers to manage them *in situ*.

The implementation of good agricultural practices (GAP) will be crucial. GAP help improve food, environmental and occupational safety, and are a key factor in sustainable agriculture. Farmers should be adequately informed and prepared to use improved seeds more efficiently and sustainably, which could help reduce the use of pesticides, herbicides, and fertilizers. New agricultural tools not only contribute to sustainable food production, but also to research and further studies. If one looks at EFSA's guidelines on the environmental risk assessment of GM plants (https://www.efsa.europa.eu/fr/efsajournal/pub/1879), most problems could be addressed by an approach centered on farmers, namely the "persistence and invasiveness of the GM plant", the "interaction of the GM plant with target organisms" and "non-target organisms", the "impact of the specific cultivation, management, and harvesting techniques", or the "effects on biogeochemical processes".

Of course, GM crops are not the only agricultural tools, but technology per se could inspire more cooperation between farmers and researchers to improve existing technologies and develop new ones. Autonomous monitoring systems and better diagnostic tools could help to identify potential or present pests (insects, fungi, bacteria, nematodes, and virus), or herbicide-resistant weeds or invasive plants. Satellite or drone-based surveillance systems would help optimize pest and weed control, irrigation, and use of fertilizers. This closer cooperation between plant science, agricultural science, and farmers could improve yield and sustainability in the developed world, and could eventually be applied to farms in developing countries to strengthen their agricultural base.

At the end of the day, farmers know best how to use the tools at their disposal. However, a costly, burdensome and illogical regulation process that prevents farmers from using important tools—new plant varieties with greater yield and greater tolerance for biotic and abiotic stress—makes it harder for them to meet important societal goals such as sustainable agriculture, and increasing yield on limited land to feed the growing human population. A new regulatory framework for GM crops should therefore operationally focus more on agriculture and, for its general objectives, seek democratic legitimation from all citizens, not just interested stakeholders.

Conflict of interest

The authors declare that they have no conflict of interest.

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